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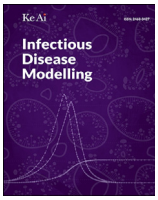

Emergence and spread of drug resistant influenza: A two-population game theoretical model

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ABSTRACT

Background: The potential for emergence of antiviral drug resistance during influenza pandemics has raised great concern for public health. Widespread use of antiviral drugs is a significant factor in producing resistant strains. Recent studies show that some influenza viruses may gain antiviral drug resistance without a fitness penalty. This creates the possibility of strategic interaction between populations considering antiviral drug use strategies.

Methods: To explain why, we develop and analyze a classical 2-player game theoretical model where each player chooses from a range of possible rates of antiviral drug use, and payoffs are derived as a function of final size of epidemic with the regular and mutant strain. Final sizes are derived from a stochastic compartmental epidemic model that captures transmission within each population and between populations, and the stochastic emergence of antiviral drug resistance. High treatment levels not only increase the spread of the resistant strain in the subject population but also affect the other population by increasing the density of the resistant strain infectious individuals due to travel between populations.

Results: We found two Nash equilibria where both populations treat at a high rate, or both treat at a low rate. Hence the game theoretical analysis predicts that populations will not choose different treatment strategies than other populations, under these assumptions. The populations may choose to cooperate by maintaining a low treatment rate that does not increase the incidence of mutant strain infections or cause case importations to the other population. Alternatively, if one population is treating at a high rate, this will generate a large number of mutant infections that spread to the other population, in turn incentivizing that population to also treat at a high rate. The prediction of two separate Nash equilibria is robust to the mutation rate and the effectiveness of the drug in preventing transmission, but it is sensitive to the volume of travel between the two populations.

Conclusions: Model-based evaluations of antiviral influenza drug use during a pandemic usually consider populations in isolation from one another, but our results show that strategic interactions could strongly influence a population's choice of antiviral drug use policy. Furthermore, the high treatment rate Nash equilibrium has the potential to become socially suboptimal (i.e. non-Pareto optimal) under model assumptions that might apply under other conditions. Because of the need for players to coordinate their actions, we

List of abbreviations: *L*, treat at a low rate; *H*, treat at a high rate; *NE*, Nash equilibria; *ODE*, Ordinary differential equation.

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conclude that communication and coordination between jurisdictions during influenza pandemics is a priority, especially for influenza strains that do not evolve a fitness penalty under antiviral drug resistance.

1. Introduction

Case importation is the primary means by which horizontally transmitted infectious diseases of humans can move between populations. For instance, the 2009 pandemic influenza A (pH1N1) viral strain originated in Mexico, but quickly spread to other countries through international travel (World Health Organizationet al, 2009). pH1N1 spread as much in 6 weeks as other influenza strains spread in six months (World Health Organization (WHO)et al., 2009). After an imported case of pH1N1 was identified in Germany on 27 April 2009 (only a month after the virus was identified in Mexico City) the global transmission of pH1N1 appeared to be on the horizon (Novel influenza A (H1N1) Investigation Team et al 2009).

If vaccines are not immediately available during an influenza pandemic, antiviral drugs are one of the most effective ways to reduce the health burden of infections (Ferguson et al., 2005). There are four types of antiviral drugs available to treat influenza: oseltamivir, zanamivir, amantadine and rimantadine (Ortiz et al., 2008). However, some factors delay the onset of treatment, and emergence and transmission of antiviral drug viruses may reduce the efficacy of treatment (Handel, Longini, & Antia, 2009). M_2 inhibitors such as amantadine and rimantadine work only against influenza A. In contrast, neuraminidase inhibitors such as zanamivir and oseltamivir are effective against both influenza A and influenza B (Winquist et al., 1999). Neuraminidase inhibitors block the function of the viral neuraminidase protein enzyme that prevents the discharge of viruses from the infected host cell and precludes new host cells from getting infected. The development of oseltamivir resistance is minimal if it is used at recommended doses for treatment (Aoki, Boivin, & Roberts, 2006). However, high rates of resistance are possible: 18% prevalence of resistance to oseltamivir has been observed among treated children in Japan (Kiso, Mitamura, Sakai-Tagawa, Shiraishi, Kawakami, Kimura, Hayden, Sugaya, & Kawaoka, 2004). Also, in 2008, a high level of emergence and spread of oseltamivir resistance viruses was observed in Europe (Meijer et al., 2009).

A number of mathematical models (primarily, ordinary differential equation models) have explored the potential impact of the emergence of drug resistant influenza and its spread during an outbreak (Moghadas, BowmanRöst, & Wu, 2008; Regoes & Bonhoeffer, 2006; Stilianakis, Perelson, & Hayden, 1998). This research has provided useful insights into the emergence and spread of drug-resistant influenza. These models predict that the final size of a pandemic can be reduced by applying an adaptive antiviral strategy with properly timed increases in drug usage, and that chemoprophylaxis of susceptible individuals is one of the best ways to reduce the force of infection of an epidemic and keep the emergence of drug resistant viruses low (Lee, Chowell, & Castillo-Chávez, 2010). A recent study (Chao, Bloom, Kochin, Antia, & Longini, 2012) presents a stochastic model of influenza. A stochastic model is a tool for assessing the impact of noise on a dynamical systems' trajectories, and generates probability distributions of possible outcomes by allowing random variation in one or more inputs over time. The importance of recognizing stochasticity relates to the fact that some characteristics of the spread of infectious diseases can depend on random events. In a small population especially, stochasticity is expected to play a significant role in epidemic dynamics, especially when the number of infected hosts is low and epidemic fade-out is likely to happen (Isham, 2004).

Most previous models on the emergence of antiviral drug resistance focus on dynamics in a single population in isolation from other populations, however, there are conditions under which decisions about antiviral drug use in one population can affect other populations, which calls for the use of tools like game theory. Game theory is the study of decision-making where players make choices that affect the outcomes (payoffs) for other players—the formalization of strategic interactions in a group (Osborne, 2004). The Prisoner's Dilemma, for instance, is a two player game in which each player can choose between two strategies, either cooperate or defect. Each player earns a high payoff r when both cooperate, but if only one of them cooperates, the one who defects will gain a very high payoff t while the cooperator will get a very low payoff s. If both defect, both receive moderate payoff u (where $t > r > u > s$). It can be shown that both players would be better off if they cooperated (since $r > u$) but what actually happens is that both players, if thinking strategically, will defect (since $t > r$). As a result, a situation where both players defect is the Nash equilibrium—the expected outcome of the game. This game captures the clash between individually optimal versus socially optimal actions. In the case of antiviral drug use during a pandemic, there may be strategic aspects of antiviral drug use decisions of multiple populations connected through travel. For instance, consider two populations connected through travel, where a decision-maker in each population must decide how antiviral drugs will be distributed in their population. Under certain epidemiological circumstances, it may make sense for the two populations to cooperate (in the sense of the Prisoner's Dilemma) with one another by both treating their infected individuals at a low level and thereby avoiding emergence of drug resistance. However, one population may defect by adopting a higher treatment level, thereby increasing the chance that a drug resistant strain is created and spread to the other population. The incentive for this strategy is the reduction in the final size of the epidemic. However, defection is available to both populations, and thus both have the incentive to defect by treating at a high level. If a drug resistant influenza strain is as transmissible as the non-

resistant strain (i.e., no fitness penalty), then it is possible for a socially suboptimal Nash equilibrium to develop where both players use antiviral influenza drugs at a high rate, when the socially optimal behaviour is actually for both players to treat at a low rate. Because the evolution of antiviral drug resistance without a fitness penalty has been observed (Bloom, Ian Gong, & Baltimore, 2010; Butler et al., 2014), this is a possibility that should be explored in mathematical models.

Most previous game theoretical analyses in epidemiology have looked at vaccinating decisions or social distancing decisions (Bauch & Earn, 2004; Geoffard & Philipson, 1997; Reluga, 2010), although strategic, multi-population aspects of antiviral drug use during a pandemic has explored this interaction in a limited setting in Jnawali, Morsky, & Bauch, (2016). This previous research assumes a 2-player, 2-strategy game where each player can only adopt one of two strategies: low treatment rate or high treatment rate. The payoffs of the model were fixed parameters representing final epidemic sizes for the four strategy combinations. This research showed how to formalize strategic interactions in antiviral drug use, and explored some of the possible consequences. For instance, conditions for two Nash equilibria were determined (i.e., both Defect-Defect and Cooperate-Cooperate are Nash equilibria), and it was also found that travel connections had a great impact on possible strategic outcomes such as defection or cooperation. However, the previous analysis was limited because of three simplifying assumptions: it did not use a disease transmission model to determine the final epidemic sizes and therefore the payoffs; players were limited to choosing between two discrete levels of antiviral drug use; and the approach did not capture stochasticity in disease transmission. As a result of the first and third limitations in particular, the existence of two Nash equilibria as might occur in a coordination game could not be deduced with as much confidence as would be permitted by a mechanistic stochastic model of disease transmission and emergence of antiviral drug resistance.

Here, we relax these three simplifying assumptions of the previous research by developing a mechanistic, stochastic disease transmission model to study this strategic interaction, still in the context of a 2-player game theoretical model. The players—decision-makers in the two populations who limit antiviral drug supply and therefore determine usage levels—may pick from a set of strategies; the strategies chosen by each player determine the payoffs. The set of strategies that each population may choose from are the treatment rate of infectious persons. For each treatment rate there is a payoff as a function of the final size of the epidemic in that population. A population can treat their citizens once they get infected. However, a population cannot treat infectious people from the other population, and thus is susceptible to imported infections. Further, a very high treatment level will reduce the final size of the regular strain, but will increase the chances that a mutant strain is created and possibly spread to the other population as well. This dynamic is thus similar to the Prisoner's Dilemma. In the next section we describe the Model structure.

2. Material and methods

2.1. Model structure

We developed a discrete time Markov model of influenza transmission, antiviral drug use, and antiviral drug resistance evolution in two well-mixed populations connected through travel. Individuals may be treated with antiviral drugs, or not treated. They may also be either infected with the regular drug sensitive strain, or with the mutant drug resistance train. The population consists of susceptible (S), infected, and recovered individuals (R). Infected individual are categorized into infected with the regular strain and untreated (I), infected with regular strain and treated (I^t), infected with the mutant strain and untreated (I_m), and infected with mutant strain and treated (I_m^t). A diagram of these interactions is depicted in Fig. 1.

The daily, one-step transition probabilities in the Markov model are:

$$P(S,I) = 1 - \left(1 - p\frac{I}{N}\right)\left(1 - p\phi\frac{I^t}{N}\right) \tag{1}$$

$$P(S,I_m) = 1 - \left(1 - p\frac{I_m}{N}\right)\left(1 - p\phi\frac{I_m^t}{N}\right) \tag{2}$$

$$P(I,R) = r \tag{3}$$

$$P(I^t,R) = r^t \tag{4}$$

$$P(I_m,R_m) = r_m \tag{5}$$

$$P(I_m^t,R_m) = r_m^t \tag{6}$$

$$P(I,I^t) = \mu \tag{7}$$

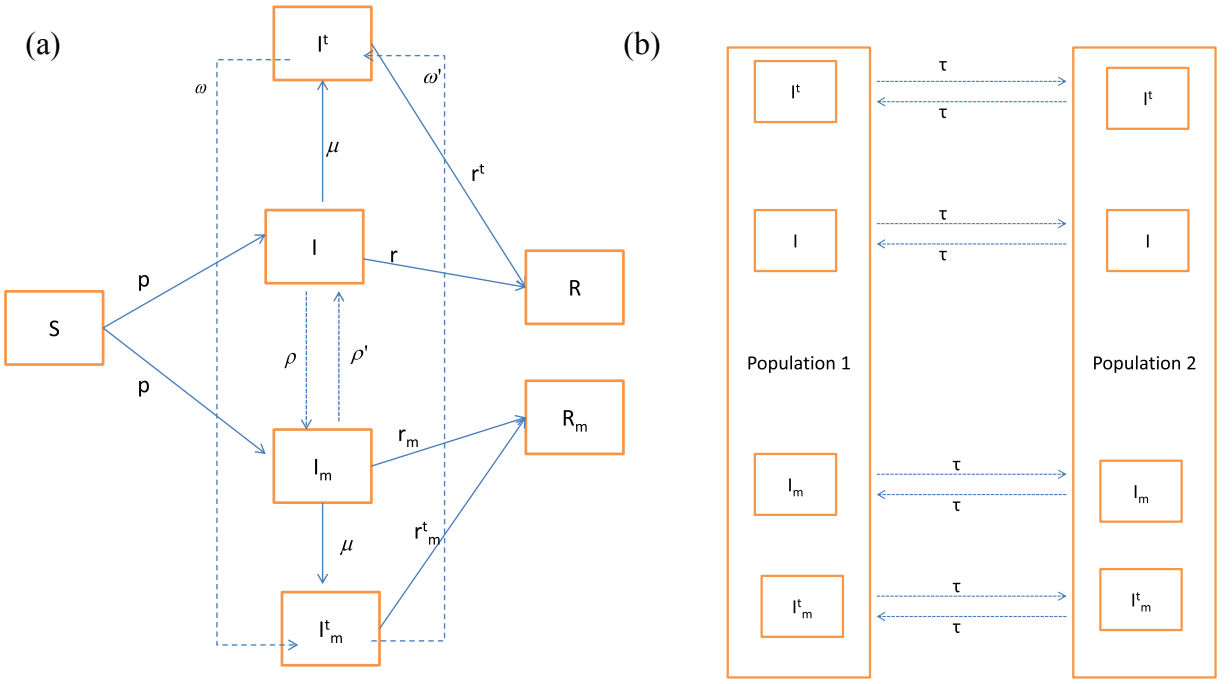

Fig. 1. Diagrammatic Illustration of the Model: (a) Compartmental model of disease transmission. The population is partitioned into three classes: Susceptible (S), Infectious (I), and Recovered (R). There are four compartments for infected individuals $\boldsymbol{I}, \boldsymbol{I_m}, \boldsymbol{I^t}, \boldsymbol{I^t_m}$ and two for recovered individuals R and R_m. (b) This diagram shows how the people of different populations go from one compartment to another.

$$P(I_m, I_m^t) = \mu \tag{8}$$

$$P(I, I_m) = \rho \tag{9}$$

$$P(I_m, I) = \rho' \tag{10}$$

$$P(I^t, I_m^t) = \omega \tag{11}$$

$$P(I_m^t, I^t) = \omega' \tag{12}$$

where $P(S,I)$ is the transition probability from the susceptible compartment (S) to the infected by the normal strain compartment (I); $P(S,I_m)$ is the transition probability from the susceptible compartment (S) to the infected by the mutant strain compartment (I_m), and similar meanings apply for the other transitions, ϕ is the relative transmissibility of treated infected individuals, and p is the probability that a susceptible-infected contact results in a new infection. All other parameters concerning disease natural history in infected persons are summarized in Table 1, and we explain each of the processes described by the above equations in the following subsections. Parameter values were set according to available literature whenever possible, or calibrated to available empirical targets. We assumed five initially infected individuals ($I(0) = 5$) unless otherwise noted.

2.2. Transmission probability and case importation

We assume that susceptible individuals can be infected by either the regular strain or the mutant strain with the same rate of transmission, p, following the observation that drug resistant influenza strains can often spread without a fitness penalty (Bloom et al., 2010; Butler et al., 2014). Influenza has a high person-to-person transmission rate. ϕ is the relative transmissibility of treated infected individual. We used the final size of the epidemic as 21% (Ross et al., 2010) to calibrate the value of p by varying p from 0 to 1 across multiple model realizations and choosing the value of p that minimized the difference $\left|\frac{R_\infty}{N} - 0.21\right|$. We repeated this grid sweep procedure until p was determined through error minimization down to three decimal places.

Table 1
Variables and Parameters, values and descriptions: We use the following parameter values as our base case for model simulations.

Variables		Description	
I		Infected untreated	
I^t		Infected treated	
I_m		Infected untreated with mutant strain	
I_m^t		Infected treated with mutant strain	
Parameters	**Description**	**Value**	**Reference**
P	Transmission between S and I	0.335/day	Calibrated
P	Transmission between S and I_m	0.335/day	Calibrated
Φ	Relative transmissibility of treated infected individual	.25–1	(Chao et al., 2012)
M	Probability of treatment	0–0.5/day	Assumption
P	Probability of mutation from I to I_m	10^{-6}/day	(Chao et al., 2012)
ρ'	Probability of mutation from I_m to I	10^{-6}/day	(Chao et al., 2012)
Ω	Probability of mutation from I^t to I_m^t	0.04/day	(Chao et al., 2012)
ω'	Probability of mutation from I_m^t to I^t	0/day	(Chao et al., 2012)
r	Probability of recovery from I to R	0.25/day	(Regoes & Bonhoeffer, 2006)
r^t	Probability of recovery from I^t to R	0.5/day	(Regoes & Bonhoeffer, 2006)
r_m	Probability of recovery from I_m to R_m	0.25/day	(Regoes & Bonhoeffer, 2006)
r_m^t	Probability of recovery from I_m^t to R_m	0.375/day	(Regoes & Bonhoeffer, 2006)
τ	Rate of infected people move from one population to another	0.01/day	Assumption

2.3. Antiviral drug treatment

Once an individual becomes infected they may be treated with some probability. The probability of treatment per unit time, μ, is the same for the regular and mutant strains. We assume $\mu \in [0,0.5]$ per day, ranging from no treatment at all to a relatively rapid treatment rate of 50% of infected cases moving into drug treatment per day ($\mu = 0.05$/day).

2.4. Natural disease history/recovery

In untreated individuals, resistance to the drug is gained with probability $\rho = 10^{-6}$ per day and lost at the same rate (Chao et al., 2012). We assume that treatment carries a small probability of generating a drug-resistant mutant strain. In treated individuals, resistance is gained with probability $\omega = 0.04$ per day and lost at ω' (we will take $\omega' = 0$ for our analysis) (Chao et al., 2012). We note the probability that antiviral drug treatment causes emergence of a drug-resistant influenza strain varies widely across subtypes, and in some cases it can even emerge *de novo*. Hence, our model is restricted to an influenza strain where *de novo* emergence of drug resistance is rare, and treatment carries a very low but non-negligible probability of causing evolution of drug resistance. There are two compartments R and R_m for recovered individuals after getting infected by the regular strain and the mutant strain respectively. The probability of recovery from infected untreated to recovered is r, which is the same as the probability of recovery from infected untreated with mutant strain to recovered, r_m. Moreover, the probability of recovery from infected treated to recovered is r^t, and the probability of recovery from infected treated with mutant strain to recovered is r_m^t. We assume the inequality $r_m = r < r_m^t < r^t$ holds true (Regoes & Bonhoeffer, 2006). Once an individual recovers, s/he will no longer be susceptible.

2.5. Demographic processes

We ignored the birth and death rate throughout the whole epidemic, since the timescale of birth and death is very slow compared to the timescale of an epidemic. We let both populations have an equal number of 100,000 individuals. Air travel has greatly accelerated the spread of influenza and other diseases transmitted by person-to-person contact. As an example, populations with a higher volume of airline travel to and from Mexico experienced earlier outbreaks of pandemic H1N1 2009 (Kenah, Chao, Matrajt, Elizabeth Halloran, & Longini, 2011). Therefore we assume that infectious individuals can transmit to susceptible individuals living in the same locale, or to susceptible individuals in another population by traveling at a per capita rate τ. Infected persons can also travel, since many individuals infected with influenza can be either pre-symptomatic or asymptomatic, We assumed that τ is the same for both populations (i.e. traveling rate from population 1 to population 2 and vice-versa).

2.6. A two population game

The strategic interaction between the two populations was formulated as a classical two-player game where each player is characterized by a strategy set and payoff functions describing the payoff for a given strategy, contingent on what strategy the other player chose. Using these assumptions and the transmission model, the Nash Equilibrium was then determined through numerical simulation of the Markov model.

2.6.1. Game description

The players of the game are two populations, population 1 and population 2, who choose a treatment rate (per capita probability μ of treatment per unit time) for their members (or rather, we posit a central authority that recommends a policy of antiviral drug use and possibly also limits the supply of antiviral drugs accordingly). The populations may choose a treatment rate, $0 \leq \mu \leq 0.5$/day. We constrain $\mu \leq 0.5$ under the assumption that the process of visiting a physician, obtaining a diagnosis of influenza, and initiating treatment with antiviral drugs takes time, and therefore a treatment rate of more than 50% of currently infected persons per day would be unrealistic. The "currency" of the game is the final size of the epidemic of regular or mutant strains, measured by the number of individuals in the Recovered compartment at the end of the epidemic. The payoff, P_i, of population i that adopts treatment rate, μ_i, is

$$P_i\left(\mu_i, \mu_j\right) = -\alpha F_i^r\left(\mu_i, \mu_j\right) - (1-\alpha) F_i^m\left(\mu_i, \mu_j\right) \tag{13}$$

where F_i^r and F_i^m are the final epidemic size—the number of individuals recovered from infection during the outbreak—for the regular and mutant strains respectively, when population i treats at the rate μ_i and j at the rate μ_j α is the weighting factor which is used to control and balance the priorities of preventing infection by both strains. We constrain $\alpha < 0.5$ under the assumption that the mutant strain is less desirable than the regular strain, either on account of being drug-resistant or perhaps also on account of being more virulent. We note that the payoff function is negative, because maximizing payoff for a currency such as this is the same as minimizing harmful health impacts. Alternatively, one could formulate the currency in terms of some health-quality units such as quality-adjusted life-years (QALY), and subtract the QALY impacts of infection from a baseline QALY representing average remaining quality-adjusted life-years of a typical individual (Wells, Klein, & Bauch, 2013). However, this would amount to the same expression as Eq. (13).

2.6.2. Nash equilibrium

If each player has chosen a strategy and no player can improve his or her payoff by changing strategies while the other players keep theirs unchanged, then the current set of strategy choices constitute a Nash equilibrium, which game theorists assume to be the strategy most likely to be adopted by all players. Here we seek to identify the Nash equilibrium antiviral drug treatment rate. Since our game is a two-player symmetric game (assuming both players have the same initial conditions of infected individuals) with continuous strategy set $0 \leq \mu \leq 0.5$, a strategy μ^* is defined as a strict Nash equilibrium if and only if

$$P_1(\mu^*, \mu^*) > P_1(\mu, \mu^*) \tag{14}$$

for any alternative strategy $\mu \neq \mu^*$, such that a higher payoff cannot be achieved by switching strategies to $\mu \neq \mu^*$. The same equation applies to population 2.

2.6.3. Algorithm for determining Nash equilibrium

To find the Nash equilibrium for the game, we use a Cournot model of best response functions. A player's best response is the strategy that produces the greatest output for him/her given that what other players are doing. A curve which joins all these points is the best response curve. A pair of solution sets to such curves is a Nash equilibrium which is the point of intersection of the curves for each player (Fudenberg & Tirole, 1991). For each value of μ_2 from 0 to 0.5, we identify $\mu_1^*(\mu_2)$ that maximizes $P_1(\mu_1,\mu_2)$. The curve composed of these $\mu_1^*(\mu_2)$'s is the best response curve of population 1 against population 2's decision of μ_2. Similarly, for all values of μ_1 from 0 to 0.5, we find $\mu_2^*(\mu_1)$ that maximizes $P_2(\mu_2,\mu_1)$. The curve of $\mu_2^*(\mu_1)$'s is the best response curve of population 2 against population 1's decision of μ_1. The Nash equilibrium is the intersection of these two best response curves.

We ran 10,000 simulations and averaged the payoff across all 10,000 simulations at each value of μ_1 and μ_2 tested, in order to find the best response for population 2 for each treatment rate for population 1. In addition, we found 100 such points for 100 different treatment rates for population 1 to produce the best response curve for population 2. Similarly, we repeat the process to find the best response for population 1 for each treatment rate for population 2. Moreover, we ran 5000 simulations for the output of other results (plots). Initially, we introduced 5 infected people in population 1 and observed closely how disease spread into population 2 in 400 days. Some parameters such as μ,ω,τ, and ϕ are varied to uncover the impact of these parameters on disease transmission and Nash equilibria.

3. Results

3.1. Epidemic dynamics

On average, for the parameter values in Table 1, the epidemic curves are fairly similar in the two populations although the epidemics start and end somewhat earlier in population 1 (Fig. 2(a)) than population 2 (Fig. 2(b)), on account of the infection being introduced first in population 1. The final size in population 1 for the regular strain is higher than in population 2, whereas the final size for the mutant strain in population 2 is higher than population 1. The epidemic peak for the regular

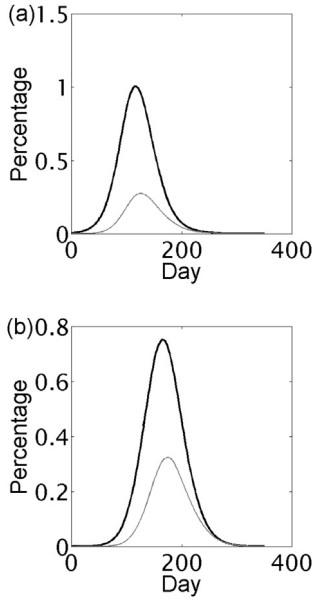

Fig. 2. The number of people infected in population 1(a) and population 2(b) in 400 days if $\mu_1 = \mu_2 = 0.035$ and $\phi = \mathbf{0.85}$. The solid black line represents the total number of infected with the regular strain while dashed grey line is for the mutant strain. Also, 5 people is infected in population 1 with total of 100,000 population.

strain is much higher than for the mutant strain in the population 1, where the epidemic began. These dynamics occur because both regular and mutant strains compete for the same pool of susceptible hosts, and recovery from one type of strain confers immunity to the other type of strain, the regular strain spreads quite rapidly before the mutant strain arises in population 1, and individuals in population 2 experience case importations of both types of strains from population 1.

Additional time series show how the epidemic unfolds for different treatment rates, μ, and mutation rates, ω in population 1 (Figs. 3 and 4). When treatment is zero, $\mu = 0$, we observed an epidemic with no mutants, as expected. For μ=0.1, we observe a greatly reduced epidemic of the regular strain, compared to the no treatment case, but we also observe a sizeable epidemic of the mutant strain. Larger treatment rates, such as $\mu = 0.2$ and $\mu = 0.3$, result in further reductions in the percentage of regular and mutant strain infections.

We also explore the average final size for regular and mutant strains as a function of the treatment rate, in population 1 (Fig. 5). The final size curve is produced for the total number of infected in 350 days in population 1. The curve shows that if the treatment rate increases then the total number of infected with the regular strain decreases gradually and goes to zero before the treatment rate reaches 0.25. On the other hand, the final size of the mutant strain increases, peaks at $\mu = 0.12$, and then declines when treatment levels are increased further. This occurs because infections with the mutant strain can not move to the compartment of individuals treated with the regular strain, since $\omega' = 0$. Supplementary Fig. S1 shows the average total population of infected with both strains in population 1 with the standard deviation above and below. It shows that the deviation decreases if the treatment level increases.

3.2. Baseline scenario

Fig. 6 depicts the best response curves for our baseline scenario (Table 1 parameter values). A player's strategy that produces the most favorable payoff if the other player's strategy is known is called a best response. The best response curve is composed of these values for the full range of possible opponent strategies. A Nash equilibrium (NE) occurs at the intersections of the best response curves of the players, since these represent points where each player cannot improve their payoff by changing strategies unilaterally. One curve is the best response of population 2 vs. population 1 and the other is the best response of population 1 vs population 2.

Here we have two Nash equilibria at $(\mu_1,\mu_2) = (0.0255,0.0345)$ (both treat at a low rate) and $(\mu_1,\mu_2) = (0.5,0.5)$ (both treat at a high rate). A strategy where both populations treat at a very high rate is a Nash equilibrium, since very high treatment rates can significantly reduce the final sizes of both regular and mutant strains (Figs. 3–5). However, a strategy where population 1 treats at a very high rate while population 2 treats at a low rate (or *vice versa*) is not a NE, since population 2 will receive case imports of the mutant strain from population 1 but will not be using antiviral drugs to reduce infections. A strategy where both populations treat at a low rate is a NE because when $\alpha < 0.5$, it is worthwhile to restrict treatment only to the severest infections and thereby avoid or limit the emergence of drug resistance, and if the other population cooperates by doing the same, then emergence of antiviral drug resistance will be avoided.

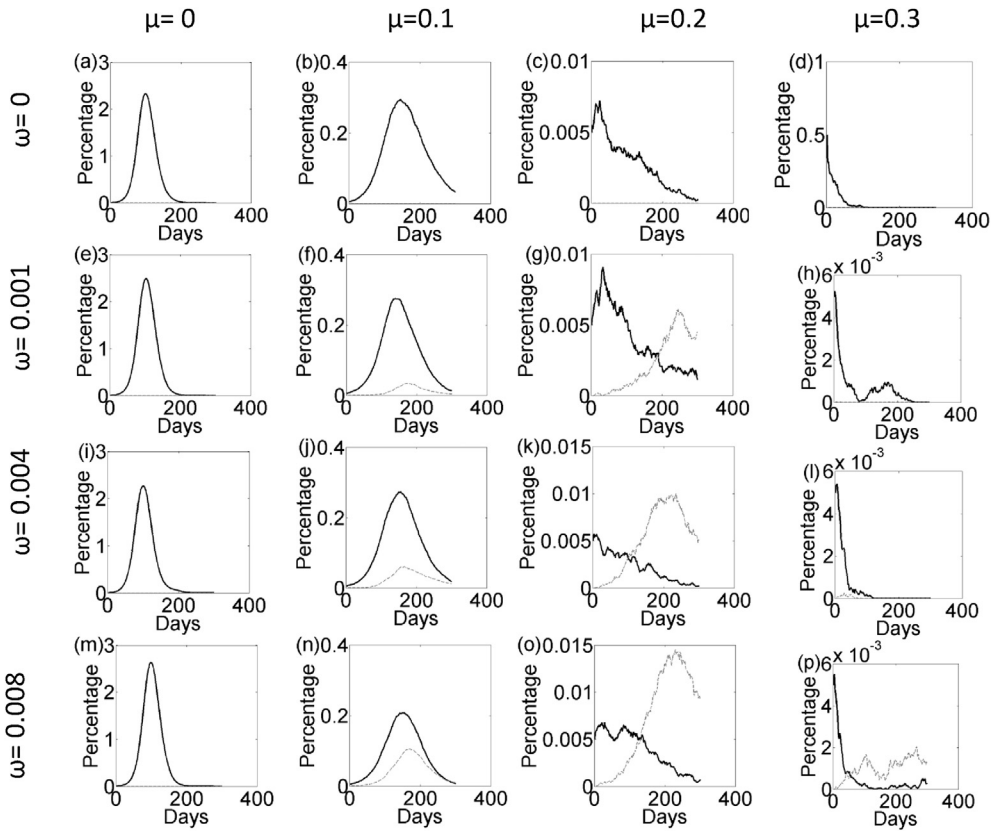

Fig. 3. Time Series Plots: This plot is produced for different treatment rate, μ and ω. Also, the solid black line represents for the regular strain and the dashed grey line is for the mutant.

3.3. Impact of travel rate (τ), mutation rate (ω), and relative transmissibility (ϕ)

We explored how the low-treatment and high-treatment NE depend on model parameter values in a series of sensitivity analyses for the travel rate (τ), mutation rate (ω) and relative transmissibility (ϕ).

In Fig. 7(a), we plot the NE versus τ. As τ increases, the low-treatment and high-treatment NE begin to converge toward one another, mostly on account of an increase in the treatment rate for the low treatment NE. The convergence occurs because when treatment rates are higher, case importations constitute a higher proportion of a population's payoff function. However, the number of case importations is not under a player's control—it is determined entirely by the strategy adopted by the other population. Therefore, for the lower treatment NE, as the travel rate increases, the number of case imports from the other player also increases for a given treatment rate, and a player shifts their own optimal treatment rate upwards since they are experiencing case imports of drug-resistant mutants anyway. As the travel rate increases to very high levels, the two populations increasingly resemble a single, homogeneously mixing population. In the limit of a single (isolated) population with a single decision-maker, there would only be a single equilibrium treatment rate that corresponds to an optimization of Eq. (13). The differences between the treatment rates of each population at the high treatment NE as well as the low treatment NE is due to the asymmetry in the initial conditions of the populations—the infection is initiated only in population 1.

Fig. 7(b) displays the NE vs ω, which shows how mutation rate affects the NE. For higher ω, the risk of generating mutants is greater, causing a decrease in payoff if mutants are generated. In contrast to the response to increasing τ, the response to increasing ω is that both high and low NE move toward lower treatment rates, while the relative difference in treatment between low and high treatment NE is roughly conserved. This occurs because when mutation rates are high, players are less willing to risk generating mutations (all else being equal) and so the NE treatment rate declines. Interestingly, the spread between low and high NE is relatively constant as ω increases, so the presence of the social dilemma is not sensitive to the value of the mutation rate, at least for the parameter values we explored.

Finally, Fig. 7(c) depicts the NE for various values of the relative transmissibility of treated individuals, ϕ. We observe that the treatment level at both low and high treatment NE is higher for higher ϕ. This occurs because if treatment is less effective in preventing transmission, there will be a higher final size of both mutant and regular strains, and hence players will wish to increase their treatment rate in an attempt to reduce the final size and prevent more cases. However, this result is also interesting and unanticipated, since higher treatment rates will also generate a higher probability of mutation to antiviral

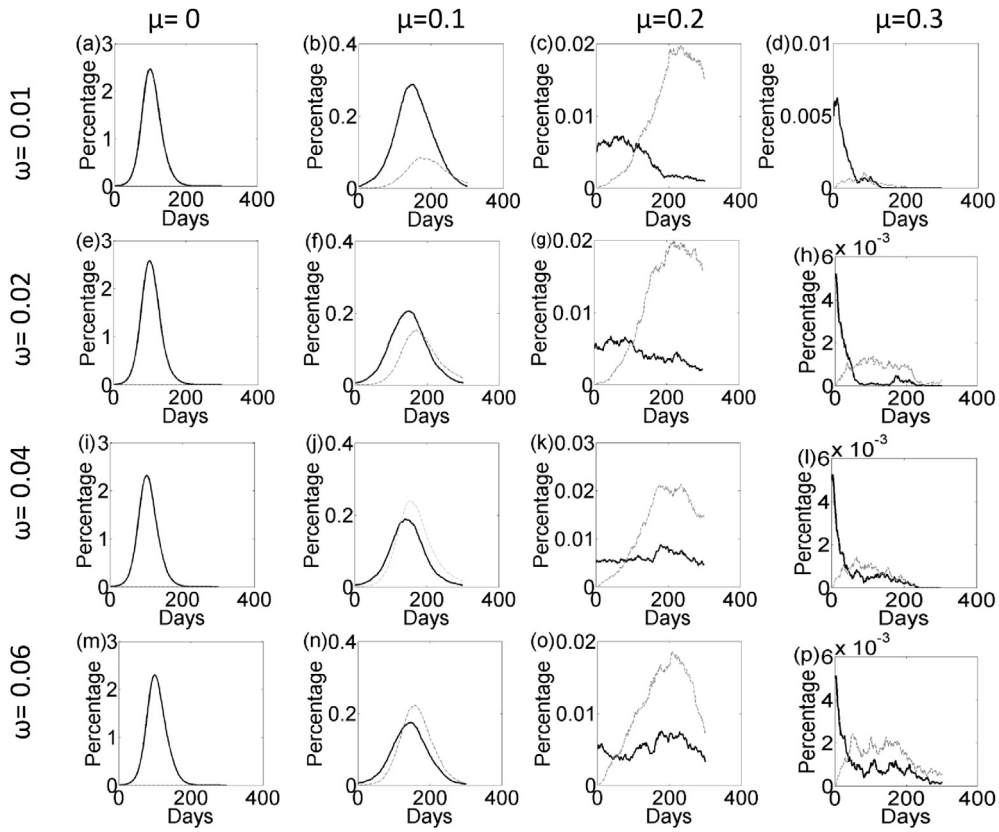

Fig. 4. Time Series Plots: This plot is produced for different treatment rate, μ and ω. Also, the solid black line represents for the regular strain and the dashed grey line is for the mutant.

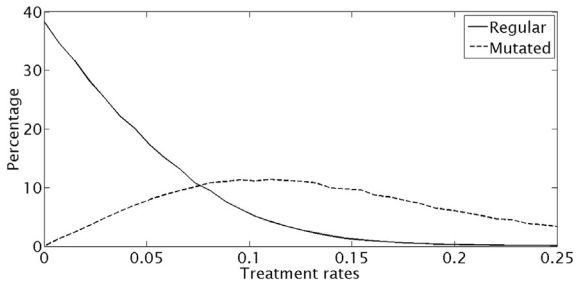

Fig. 5. Final Size Plot: The total number of people got infected in population 1 in 350 days for different treatment rate if $\phi = \mathbf{0.85}$. The solid line represents for the regular strain and the dashed line is for the mutant. See supplementary figure S1 for errorbars.

drug resistance. The optimal outcome depends on the tension between the objectives of decreasing the final size through more antiviral drug usage, versus preventing the evolution of antiviral drug resistance through less antiviral drug usage. As for ω, the spread between treatment rates at low and high NE is not significantly affected by changes in ϕ.

In summary, the existence of low- and high-treatment Nash equilibria is sensitive to the travel rate, but not the mutation rate or the relative transmissibility of treated individuals.

4. Discussion

Here we developed and investigated the predictions of a game theoretical model where two populations choose from a continuum of antiviral drug treatment rates, μ_1 and μ_2, and where each population must weigh the undesirable possibility of generating drug-resistant mutants through treatment and/or receiving case imports of the drug-resistant mutant from the other population, despite a conservative approach. The model was a stochastic, mechanistic simulation model that incorporated empirical estimates for parameter values and each population's choice was determined according to game theory.

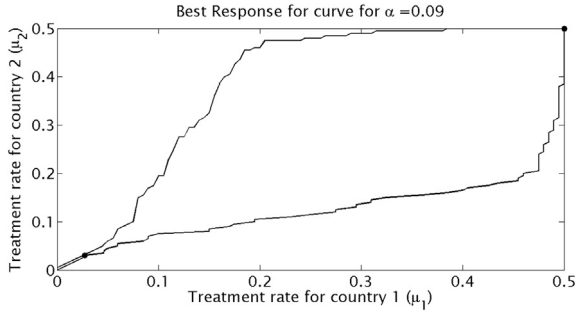

Fig. 6. Best Response Curve produced for various treatment rate for population 1 and population 2.

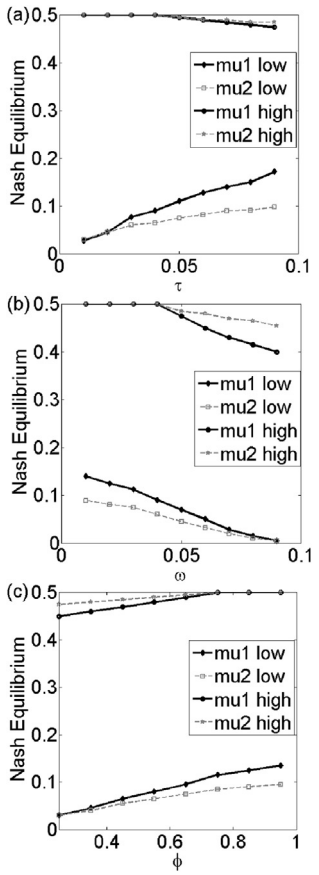

Fig. 7. High and low Nash equilibrium curve for population 1 and population 2 produced for different τ (a), ω (b), and ϕ (c). The solid black like represents for μ_1 and grey dash line is for μ_2.

We identified two Nash Equilibria, one corresponding to both populations adopting a high treatment rate and one corresponding to both populations adopting a low treatment rate. Notably a mixture where one population adopts a high treatment rate and the other adopts a low treatment rate cannot occur, according to the predictions of a Nash equilibria. They tend to both adopt high rates, or both low rates, because of the influence of the other player. Therefore this analysis shows that strategic interactions can strongly influence what treatment rate strategy a population may decide to adopt, in populations open to travel. The populations may choose to maintain a low treatment rate that does not increase the incidence of mutant strain infections or to create more resistant cases by choosing a higher treatment level.

Interestingly, because the final size for both mutant strain and regular strain are so small under the high treatment NE, the high treatment NE cannot be interpreted as a socially suboptimal Nash equilibrium, as was suggested in our previous game theoretical analysis that did not use a transmission model (Jnawali et al., 2016). However, this result depends on the assumption that the antiviral drug reduces transmission of both regular and mutant strains to an equal extent. Under other

conditions, it is known that abundant use of antiviral drugs can result in widespread transmission of the drug resistant strain, and a nontrivial final epidemic size of the resistant strain (Lipsitch, Cohen, Murray, & Levin, 2007). Under model assumptions where transmission of the resistant strain is less affected by antiviral drugs than transmission of the regular strain, the high treatment NE may therefore be socially suboptimal (i.e., non-Pareto optimal). This is a topic for future research. We also note that this work establishes the existence of two Nash equilibria more strongly than our previous research (Jnawali et al., 2016), because it is based on a mechanistic model for infection transmission and drug resistance evolution, rather than imposing fixed parameter values representing the final size and the risk of generate mutants through antiviral drug usage, for which we must then guess as to how they respond to changing treatment levels.

There are several limitations of our model, which future studies should aim to relax. For instance, in this model we only considered the first wave of an epidemic. Thus, we ignored the possibility of other waves (although our model is capable of exhibiting subsequent waves). Moreover, we only considered two populations, although in real-world pandemics, a large number of interconnected populations of differing sizes are making decisions about antiviral drug treatment. Future work could develop *N*-population models. Finally, we neglected social processes and the internal decision-making structure of each population, whereas future work could divide each population into decision-makers and influenza patients.

We used a stochastic model since all model realizations—including ones where the infection went extinct due to stochastic effects before causing a large outbreak—were used to compute payoff functions. Stochastic fade-out is an important feature of real outbreaks especially in their early stages, and in our model the emergence of an initially rare drug resistant mutant is a stochastic process that also hinges upon the adopted level of antiviral drug usage. Deterministic models are less suited to this situation since they cannot be used to predict extinction probabilities. However, it would also be worthwhile to explore whether using an ordinary differential equation (ODE) model instead would be fruitful in circumstances where stochastic effects are not important, since ODEs are easier to analyze and thus can generate more insight.

5. Conclusions

We conclude that, because influenza can evolve resistance without a fitness penalty, strategic multi-population interaction should be further studied. Furthermore, because of the potential for socially suboptimal outcomes in situations where fitness penalties do not arise and for parameter values permitting higher rates of mutant transmission at high rates of antiviral drug treatment, this work suggests the need for better inter-jurisdictional coordination in the event of future influenza pandemics.

Competing interests

CTB has received research grants from GlaxoSmithKline Vaccines for the study of influenza vaccination.

Authors' contributions

KJ designed the model, analyzed the model, and wrote the manuscript. BM contributed to model analysis and writing the manuscript. KP contributed to model simulations and analysis. CTB conceived the study and contributed to model design, analysis, and writing the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.idm.2016.07.003.

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